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LETTER TO THE EDITOR

Reply: The role of *DNAJB2* in amyotrophic lateral sclerosis

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Sir,

Heat shock proteins (HSPs) are protein chaperones that play important roles in maintaining protein homeostasis. Ours and others' research have shown that *DNAJB2a* (encoded by *DNAJB2*) is capable of resolving aggregates caused by TDP-43 (Chen *et al.*, 2016), SOD1 (Novoselov *et al.*, 2013; Gess *et al.*, 2014), huntingtin (Labbadia *et al.*, 2012) and mutant parkin (Rose *et al.*, 2011). Given *DNAJB2*'s neuronal enriched expression, it is not surprising that it shows such effectiveness in resolving the protein aggregates associated with neurodegenerative diseases. The question is, is *DNAJB2a* the sole protein for that role, and is *DNAJB2a* there to perform such function in the case of neurodegeneration.

ALS is the neurodegenerative disease that most prominently affects motor neurons. It is a heterogeneous disorder where the majority of affected individuals have no family history of ALS. Nevertheless, TDP-43 proteinopathy (i.e. presence of insoluble, hyperphosphorylated, cytosolic TDP-43 aggregates) is found as a common phenotype in affected tissues in ALS with or without mutations in TDP-43. This pathological feature is also seen in ~60% of FTD which supports the idea that FTD and ALS are on the same disease spectrum. We agree with Frasquet *et al.*'s conclusion that it would be interesting to study the genetic contribution of *DNAJB2a* to ALS, but if we do find any, we predict they would be quite different than the ones found in distal hereditary motor neuropathy (dHMN).

The known *DNAJB2a* mutations in association with dHMN are c.352 + 1G > A (Blumen *et al.*, 2012; Frasquet *et al.*, 2016) and c.229 + 1G > A (Gess *et al.*, 2012), both of which are autosomal recessive mutations altering the splicing

of *DNAJB2* and lead to reduced protein expression. However, in our unpublished study, we did not find the loss of *DNAJB2* *per se* is sufficient to trigger TDP-43 aggregation. On the contrary, our data show that HSF1(+) still refolds TDP-43 when *DNAJB2a* is knocked down (unpublished data). This result suggests that there are some functional redundancy of HSP, and *DNAJB2a*, although is capable in refolding TDP-43, is not the only HSP for this task. Thereby, a simply loss of *DNAJB2* is unlikely to cause TDP-43 proteinopathy that is associated with ALS and FTD. However, as we proposed in our original paper, it does appear that the heat shock response as a whole is compromised in ALS due to a yet to be determined cause. It will be of great interest to investigate the genetic contribution from not only *DNAJB2a*, but any HSPs and also HSF1.

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